(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complements of (a) and (b).

Remarks

Applicants have amended the claims to clarify the claim language and have added a new claim to claim specifically the subject matter disclosed in U.S. application no. 09/060,706. Applicants also have amended the specification in view of the objections to the specification. The amendments to claim 9 are supported in the specification at page 15, lines 10-13 and page 14, lines 2-6. No new matter has been added.

Objections to the Specification

Applicants have amended the specification to eliminate the typographical error on page 1 and to remove the hyperlink text on page 12. Reconsideration is respectfully requested.

Claims Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claim 1, 8, 9, 18, 19 and 51-56 as lacking an adequate written description. Applicants respectfully request that the Examiner withdraw the rejection for the following reasons. The written description of the invention in the specification as filed teaches one of ordinary skill in the art how to make and use the claimed invention throughout its scope (see below). Given that the invention was enabled by the specification as filed, the invention was also fully described at the time of filing in full, clear, concise and exact terms. Thus Applicants were in possession of the claimed invention at the time of filing and the invention was placed into the possession of one of ordinary skill in the art by the written description contained in the specification as filed. Furthermore, Applicants disclosed many fragments of nucleic acid and polypeptides in the application as described in more detail below.

The Examiner states that one of ordinary skill in the art would not know that Applicants were in possession of the invention because the specification does not describe the various elements of a gene containing the claimed sequences. Applicants did not claim "genes" containing the disclosed sequences; rather, the claims at issue are specifically directed to "isolated nucleic acid molecules" that have the specific sequences. One of ordinary skill in the

art would know that Applicants, having provided specific nucleotide sequences and teachings regarding isolation of nucleic acids having such sequences, were in possession of the invention as of the time of filing of the application.

The Examiner also stated that a further reason for rejecting the claims was that the specification does not provide a disclosure of the function of open reading frames contained in the nucleic acid molecules. Applicants do not understand why the function of open reading frames (i.e., proteins) is pertinent to a determination of adequate written description of nucleic acid molecules. It is enough that Applicants have disclosed the sequence of open reading frames; the notion that the claims are not adequately described because they encompass nucleic acids encoding different proteins, e.g., fragments, does not mean that the claimed subject matter is not adequately described. Moreover, with respect to fragments, Applicants extensively described fragments of nucleic acids and polypeptides (see, e.g., pages 13-17, page 26). Given Applicants description of the specific sequences claimed and extensive disclosure of the features of the claimed molecules, one of ordinary skill in the art would understand that Applicants were in possession of the claimed invention.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of the claims for inadequate written description.

The Examiner rejected claim 40 under 35 U.S.C. §112, first paragraph as not enabled. Applicants respectfully disagree with the Examiner's conclusions for the reasons put forth below.

The expression patterns for sdph3.10 and sdp3.5 are appropriate for tumor associated genes, and a considerable amount of evidence is presented in the instant application indicating that these nucleic acid molecules (sdph3.10 and sdp3.5) are heretofore undescribed members of the well-established group of tumor associated genes. The existence of tumor associated genes is well known and accepted in the art. Is it not necessary for the Applicants to establish the roles played by sdph3.10 and sdp3.5 in the development of cancer, but rather to indicate that there is potential, that would be reasonable to one of ordinary skill in the art, that the antisense can be used in the treatment of cancer. Given that the invention is clearly within the art-accepted parameters of tumor associated genes, it is sufficient to demonstrate a reasonable expectation of success in the use of the invention by one of ordinary skill in the art.

The Examiner states that it is "unclear whether a therapeutic effect would exist for the antisense." Applicants respectfully submit that such an effect need not be "clear"; the appropriate test for an enablement analysis is whether one of ordinary skill in the art would be required to use undue experimentation to practice the invention. Accordingly, requiring Applicants to have demonstrated a therapeutic effect as of filing of the application is an inappropriate standard.

One example of the utilization of antisense to block tumor growth *in vivo* (of many in the art) can be found in Sharma et al, Antisense Targeting of Perlecan Blocks Tumor Growth and Angiogenesis *In Vivo, J. Clin Invest.* 102(8):1599-1608, 1998. This publication clearly indicates that at a time prior to the filing date of the instant application, the teaching in the art included the use of antisense in modulating tumor progression and cancer treatment.

The example cited above, along with numerous other publications in the literature, clearly indicate that in the pharmaceutical arts at the time of filing the instant application, the use of antisense in therapeutic applications for cancer and other disorders was a matter or routine experimentation for one of ordinary skill in the art.

The Examiner cited Rojanasakul (published in 1996) as an additional basis for the rejection of claim 40. Rojanasakul's opinion is that the use of antisense has been *limited*, oligonucleotides *may* not reach target sites, and there is *potential* toxicity. All of these are *possible* difficulties, but Applicants contend that these hypothetical situations do not in and of themselves preclude the use of antisense in cancer treatment. The "potential for challenges to the successful utilization of these compounds" in no way negates their use by those in the art. Moreover, progress made in the art after the publication of this reference with respect to the use of antisense molecules supports a more optimistic view of the use of antisense than that put forth by Rojanasakul.

Further, the Examiner has not properly performed an analysis of the *Wands* factors as required under the law for enablement evaluations. Assuming for the moment that the Examiner has met the burden of providing reasons for doubting the assertions made by Applicants, and taking into consideration the Examiner's statements with respect to undue experimentation, Applicants still maintain that the claimed invention is enabled. Determination of undue experimentation follows from the analysis of the eight *Wands* factors. It appears that only some of these factors were considered by the Examiner (although they were not described as such);

however, all of the factors must be considered for a proper analysis and a finding of nonenablement must based on the evidence as a whole. *In re Wands* 858 F.2d 731, 737, 740, 8 U.S.P.Q.2d 1400, 1404, 1407 (Fed. Cir. 1988). Applicants maintain that full consideration of each and all of the *Wands* factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practicing the invention would not require undue experimentation.

The Examiner has apparently considered the predictability of the art, although perhaps using an excessively stringent standard. In contrast to the Examiner's assertions of unpredictability of antisense compositions, solely relating to therapeutic applications, the predictability of the art as a whole for this aspect of the invention is high. One of ordinary skill in the art can reliably predict, make and test antisense nucleic acid molecules as disclosed in the application. Numerous model systems (both cellular and whole organism) were available at the time of filing to test various aspects of antisense efficacy. For example, one can test the antisense compositions in cells to determine the effect on expression of the specific genes, as well as to test the effect on cancer phenotype. Tumor bearing animals also can be tested in a similar fashion. It is predictable from these and other possible routine experiments that one can determine antisense effect and/or efficacy.

The Examiner did not consider the remaining *Wands* factors: 1) existence of working examples, 2) guidance presented, 3)quantity of experimentation, 4) breadth of the claims, 5) the nature of the invention, 6) the state of the prior art, and 7) the level of one of ordinary skill in the art. Applicants submit that none of these factors would weigh against a finding of enablement for the claimed invention. For example, very little experimentation is required to make, test and use antisense nucleic acid polypeptide molecules once the sequences of those molecules are provided, as was done in the instant application.

Applicants maintain that adequate examples and guidance were provided. Applicants provided extensive descriptions of antisense nucleic acids (see, e.g., pages 21-23), including various portions of the disclosed nucleic acids, modified oligonucleotides, etc. Methods for testing the function of the antisense nucleic acids were well known at the time of filing and Applicants cited several antisense references which provide such methods. These descriptions provide sufficient guidance to one of ordinary skill in the art at the time of filing (in 1998) to make and use the claimed antisense nucleic acids. With respect to the working examples *Wands* factor, the court in *Wright* stated that "Nothing more than objective enablement is required, and

therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* at 1561 *citing In re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicants have provided not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative examples as noted above. Thus the examples and guidance presented are not, by themselves, sufficient reasons to find undue experimentation.

The quantity of experimentation that would be required to practice the claimed invention is not excessive. Rather, the nature and quantity of such experimentation is completely routine in the relevant art. Selecting antisense nucleic acid molecules, and testing such molecules, are standard experimental procedures in molecular biology. For example, given the state of the art, one of ordinary skill in the art would only use routine experimentation to generate a series of antisense molecules and test them in cells and/or animal systems. Based on the results obtained, additional rounds of experimentation could focus on preferred molecules or variants having modified nucleotides as disclosed in the application. Such experimentation is routine as shown by the cited references and numerous other references publicly available at the time of filing of the application. Accordingly, any experimentation required would not be undue.

The claims are not excessively broad. Applicants have claimed antisense compositions based on the disclosed nucleic acid sequences, which bind to and reduce the expression of such sequences. The nature of the invention, antisense compositions, is well known to one of ordinary skill in the art.

The last two *Wands* factors are crucial to any determination of undue experimentation. In the *Wands* case, for example, the court's decision turned on the "high level of skill in the art at the time the application was filed", and that "all of the methods needed to practice the invention were known." *Wands* at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and therefore must weigh heavily in favor of a finding that undue experimentation is not required.

The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. As the court stated in *In re Howarth*, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*,

654 F.2d 103, 105 (C.C.P.A. 1981). Thus the level of knowledge of one of ordinary skill in the art cannot be ignored in the *Wands* factor analysis. For the standard procedures contemplated in the application, the level of skill in the art is high. Applicants maintain that the person of skill in the art of molecular biology or medicine would know how to prepare, test and use the claimed antisense nucleic acid compositions.

In summary, a full analysis of the *Wands* factors favors a conclusion that only routine experimentation would be required of one of ordinary skill in the art to practice the claimed invention throughout its scope.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112, first paragraph.

Claims Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1, 18, 19, 40, 41, 43, 51-58 under 35 U.S.C. 112, second paragraph as being indefinite.

The Examiner rejected claims 1 and 40 based on the premise that the recitation "...hybridization under stringent conditions..." is not clear. The Examiner stated that the claims were not clear because the specific limitations were not recited in the claims. Applicants respectfully traverse the rejection.

First, Applicants are of the understanding that claims are interpreted in view of the specification, not in a vacuum. Thus the disclosure of specific sets of conditions in the specification serves to define clearly the claim term "stringent conditions" when the claims are read in combination with the specification.

Second, Applicants maintain that "stringent hybridization conditions" is a term of art which is well-recognized by those of ordinary skill in the art. Applicants have set forth stringent hybridization conditions, explicitly and by reference to well known reference texts. However, Applicants should not be limited to these exact conditions because one of ordinary skill in the art knows of hybridization conditions of equivalent stringency which would serve equally well, as Applicants noted in the specification.

The Examiner also rejected claim 40 because the meaning of the recitation "...reduced the expression..." in claim 40 was deemed unclear. Random House Webster's Dictionary (The

Ballantine Publishing Group, Random House, N.Y., N.Y., 1998. pg. 602) defines reduce as: to bring down, as to a smaller size or amount. Applicants submit that this common, accepted definition clearly delineates the meaning of the word "reduces" in the context of claim 40 to mean the level of expression is brought down, as to a smaller amount. This notion would be clear and definite to one of ordinary skill in the art.

The Examiner rejected claims 41 and 43 because the meaning the recitation "...polypeptide precursor..." was deemed unclear. Applicants submit that the term polypeptide precursor is defined on page 11, lines 8-11 of the specification, as reproduced here:

> Such nucleic acids are termed tumor associated polypeptide precursors, and may be DNA, RNA, or composed of mixed deoxyribonucleotides and ribonucleotides. The tumor associated polypeptide precursors can also incorporate synthetic non-natural nucleotides.

Applicants believe that this definition clearly sets forth the meaning and scope of the polypeptide precursor in the context of the instant application.

The Examiner rejected claims 57 and 58 in that the meaning of the recitation "...at least a portion..." in claims 57 and 58 are vague and indefinite. Random House Webster's Dictionary (*Id.* at 557) defines a portion to be: a part of a whole; segment. Applicants submit that this common, accepted definition clearly delineates the meaning of the word "portion" in claims 57 and 58 , which encompasses all possible lengths of the designated nucleic acid that are smaller than the designated nucleic acid and larger than an amplified product of two nonoverlapping 12-32 nucleotide primers as claimed in claim 41. The bounds of "at least a portion" thus are clear and definite.

Rejections Under 35 U.S.C. § 101

The Examiner has rejected claims 1, 8, 9, 18, 19, and 51-56 under 35 U.S.C. §101 because the claimed invention is not supported by a credible utility or a well established utility. Applicants respectfully traverse the rejection.

According to 35 U.S.C. §101, an invention to be patentable must have one or more utilities, which has been interpreted to mean that either a specific and credible utility, or a well

established utility must be provided in a patent application. *Manson v Brenner* 383 U.S. 519, 148 USPQ 689 (1966); *Nelson v Bowler* 626 F.2d 853, 206 USPQ 881 (C.C.P.A. 1980). Establishment of one utility is sufficient to meet the statutory utility requirement. *Rey-Bellet v Englehardt* 493 F.2d 1380, 1383, 181 USPQ 453, 454 (C.C.P.A. 1974). As defined in the PTO Utility Guidelines, a specific asserted utility is "a practical utility which defines a 'real world' context of use." Utility Guidelines §III, USPTO. The PTO Utility Guidelines state that credible with respect to utility "refers to the reliability of the assertion of utility based on the logic and facts offered by applicant to support the assertion." Utility Guidelines §IV, USPTO. As defined in the PTO Utility Guidelines, a well established utility is "a 'specific utility' which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art." Utility Guidelines §VI, USPTO.

Applicants have provided well-established utilities. The description of the sdph3.10 (SAGE) and sdp3.5 nucleic acid molecules in the specification makes immediately apparent to one of ordinary skill in the art several specific utilities. For example, the nucleic acid molecules and polypeptides can be used in the diagnosis or treatment of conditions characterized by the expression of a tumor associated gene. Further. the SAGE and sdp3.5 polypeptides can be used to generate antibodies to SAGE and sdp3.5, and can be used as controls or standards for isolation and/or purification of the SAGE and sdp3.5 from biological extracts (e.g., by chromatography). These are well established utilities, and are well known, would be immediately apparent to one of ordinary skill in the art, and implied by the specification

Applicants have also provided specific credible utilities. On page 14, lines 17-22, Applicants state that the claimed invention "can be employed to produce nonfused fragments of the tumor associated polypeptides, useful, for example, in the preparation of antibodies, and in immunoassays". Other specific credible utilities for the use of the SAGE and sdp3.5 polypeptides encoded by the claimed nucleic acids are described on page 16, lines 23-26 which states that they can be utilized "alone or as fusion proteins to generate antibodies, as a component of an immunoassay or diagnostic assay, as therapeutics, or for determining the binding specificity of HLA molecules and/or CTL clones for sdph3.10 or sdp3.5 proteins". The claimed nucleic acids also can be used in PCR amplification as provided in the specification at page 15, line 17 through page 16, line 4. Applicants believe that these utilities meet the standard

for credible utilities, because (1) a specific stated utility creates a presumption of credibility and (2) because the Examiner has not shown that "it is more likely than not that a person skilled in the art would not consider credible any specific utility asserted." Utility Guidelines §IV, USPTO.

Although a single utility is sufficient to meet the statutory requirement for utility, other utilities are also provided, including utilization of antisense oligonucleotides that selectively bind to a tumor associated gene nucleic acid molecule, including those encoding a sdph3.10 or sdp3.5 protein, to decrease transcription and/or translation of tumor associated genes." (page 21, lines 14-27.

The Examiner's assertions with respect to the characterization of the claimed nucleic acids are not understood. For example, contrary to the Examiner's statements, Applicants clearly provided tissue and tumor distributions of the sdph3.10 and sdp3.5 gene products (see Example 2, Tables II and III and Example 4, Tables IV and V). Thus the working examples directly contradict the Examiner's reasons for asserting a lack of specific, credible or substantial utility.

The statutory utility requirement requires the establishment of only one utility. *Rey-Bellet* 493 F.2d at 1383. Applicants have provided several utilities for sdph3.10 and sdp3.5. The Examiner has not presented any arguments as to why all of the asserted utilities are not believable. Thus, the Examiner has not met the burden for a *prima facie* showing of lack of utility for the claimed invention, and it is respectfully requested that the rejections of the claims for lack of utility be withdrawn.

The Examiner also rejected these claims under 35 U.S.C. § 112, first paragraph because one of ordinary skill in the art would not know how to use the claimed invention in view of the alleged lack of asserted utility. The rejection, which the Examiner bases solely on the aforementioned 35 U.S. C. § 101 rejection, should be reversed based on the clear evidence of multiple utilities outlined above. Therefore, Applicants respectfully request that the 35 U.S.C. § 112 rejection of the claims based on the lack of utility be withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 1, 9, 18, 19, 50 and 59 under 35 U.S.C. § 102 as anticipated by GenBank accession numbers U89672 and AA213817; the Rees et al.

BioTechniques publication; and U.S. patents 5,880,102 and 5,464,745. Applicants have amended claims 1 and 9 to obviate the rejections.

Applicants comment that the Examiner did not provide specific rejections based on the specific sequences of the cited references alleged to anticipate the claimed sequences, with the exception of the GenBank sequences (only the GenBank sequences were matched to the claimed sequences by sequence identity). Accordingly, Applicants have responded as much as is possible given the lack of specificity of the rejection, but would appreciate clarification of the rejections based on Rees et al and the U.S. patents, as well as a full, non-final opportunity to respond to these rejections when more clearly set forth.

Amended claim 1 requires that the nucleic acids encode a sarcoma associated antigen. None of the references cited by the Examiner teach nucleic acids that encode such proteins. For example, U89672 is a non-coding portion of a bicistronic cloning vector, pIRES1hyg. Rees et al. is the literature reference that describes the use of this vector. The sequences in the cited US patents are also vectors (pTOPE -1B(+) for the '745 patent; an unknown vector for the '102 patent, as SEQ ID NO:1 is not described in the patent and does not apparently match any of the lengths of the sequences in the Figures of the '102 patent). AA213817 is an EST from a germinal center B cell tumor. Accordingly, claim 1 and claims which depend therefrom are not anticipated by any of the cited references.

Claim 9 has been amended to exclude the two GenBank references. This amendment was expressly supported in the specification; the cited accession numbers are present in Table VII which lists sequences homologous to SEQ ID NOS:38 and 43, portions of which are excluded from the nucleic acid sequences of the invention. Claim 9 also was amended to recite the unique fragments relate to sequences that encode sdph3.10 or sdp3.5 polypeptides. Accordingly, claim 9 and claims which depend therefrom are not anticipated by any of the cited references.

Applicants respectfully request that the Examiner reconsider the rejections of the claims under 35 U.S.C. § 102 in view of the amendments made to the claims and the statements made above.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 41 and 57 under 35 U.S.C. § 103 as obvious in view of GenBank accession number U89672; the Rees et al. *BioTechniques* publication; or U.S. patent 5,880,102. Applicants respectfully traverse the rejections.

First, the references, taken together, do not teach the limitations of the claimed invention. Claim 41 is a kit "for detecting the presence of the expression of a tumor associated polypeptide precursor". As noted above, Rees and the U89672 reference relate to the same sequence. None of the recited references teach sequences that would permit such a kit to be made.

Second, one of ordinary skill in the art would not be motivated to combine the references to make the claimed invention, a kit for amplifying a tumor associated antigen nucleic acid for detection purposes, from the teachings of the cited references. The references provide sequences of portions of cloning and (presumably for the '102 patent) expression vectors. The teachings of the references suggest the usefulness of the vectors for cloning (and possibly expression), not as substrates for nucleic acid amplification reactions for detecting expression of tumor specific nucleic acids. This is in contrast with the disclosure of the instant application with respect to the usefulness of the claimed kits. There would be no motivation for one of ordinary skill in the art to assemble a kit to provide a set of reagents for amplifying tumor antigen nucleic acids from the recited references.

The Examiner rejected claims 43 and 58 under 35 U.S.C. § 103 as obvious in view of GenBank accession number AA213817; the Rees et al. *BioTechniques* publication; or U.S. patent 5,464,745. Claim 43 has been amended and Applicants assert that the claim as amended is not obvious over the cited references.

AA213817 teaches a particular EST sequence that was isolated from germinal center B cell tumor. The invention as claimed recites a kit for detecting a tumor associated polypeptide precursor encoded by SEQ ID NO:43. One of ordinary skill in the art would not be motivated by the disclosure of AA213817 to make a kit to detect the expression of a tumor associated polypeptide precursor encoded by SEQ ID NO:43. Neither Rees et al. nor the '745 patent provide the elements missing from AA213817.

In view of the amendments to the claims and the statements made above, Applicants respectfully request that the Examiner reconsider the rejections of the claims under 35 U.S.C. § 103.

Applicants respectfully request reconsideration of the claims in view of the amendments and reasoned statements made above. If the Examiner wishes to advance the prosecution in any way, or if the amendment is defective or unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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